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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,124	07/25/2003	Maria Tang	10302.200-US	4207

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,124	TANG ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 12/2/05 is made. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50-73 are currently pending.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 20 are vague and indefinite due to the phrase "A method of producing a heterologous biological substance....wherein the mutant cell comprises a first nucleic acid sequence encoding a heterologous protein, wherein the heterologous protein is the heterologous biological substance *or the heterologous protein is involved in the synthesis of the heterologous biological substance*" is vague and confusing. The method recited in steps (a) and (b) appears to be a method of recombinant protein production, yet the new limitation does not convey this fact. The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell

or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. Accordingly, the way the claim has been amended, e.g., *or the heterologous protein is involved in the synthesis of the heterologous biological substance,* does not convey that the method is completed at step (b). If the *"heterologous protein is involved in the synthesis of the heterologous biological substance",* then how is the heterologous substance recovered from the cultivation medium at step (b) as it would not have been made yet. Clarification and correction is required.

Response to Applicants' arguments:

Applicants argue that the heterologous biological substance may be encoded by a single gene and that the product of the gene may be involved in the synthesis of a biological substance. This is understood; however, the method is to the production of the product, e.g., the protein/enzyme, regardless of what this protein/enzyme may later be involved in producing. The heterologous biological substance is not produced by the method in Applicants scenario/explanation. The method stops at the production of the gene product. This is why the preamble should be amended to state the production of a 'heterologous protein" and not a 'heterologous biological substance". As stated above, the instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is

taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The claimed methods are to using these genes minus the undesirable trait of red pigment to produce the heterologous protein, not to produce a substance the protein may later make. The latter is an entirely different method. The claimed method does not produce this subsequent substance which may be made by the recombinantly produced protein, e.g., it only makes the enzyme. Clarification and correction of the claim is required.

Claim 20 is vague and confusing because of the phrase "comprising a modification of at least one of the genes cypX and yvmC". The mere recitation of a name, i.e., cypX and yvmC, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, e.g., cypX comprising the nucleotide sequence set forth in SEQ ID NO:1 and yvmC comprising the nucleotides sequence of SEQ ID NO:8, to adequately define the genes. These sequences are critical limitations. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim 20 is vague and indefinite because of the term "heterologous biological substance". The term "heterologous biological substance" is vague and indefinite. It is unclear what substance other than a protein could be made from the claimed

transformed host. "Heterologous biological substance" is extremely vague and indefinite and could read on ***any*** biological substance not present in *Bacillus*, e.g., oil, blood, mucus, etc..

In claim 20 "modification" should be changed to "mutation" and specifically recite that the mutation results in loss of red pigment production. The claim does not directly correlate the mutation to the loss of pigment. Correction is required.

Claim 39 is vague and indefinite because of the term "heterologous biological substance". The term "heterologous biological substance" is vague and indefinite. It is unclear what substance other than a protein could be made from the claimed transformed host. "Heterologous biological substance" is extremely vague and indefinite and could read on ***any*** biological substance not present in *Bacillus*, e.g., oil, blood, mucus, etc..

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the mutant of a parent of *Bacillus* cell has not been 'obtained' as required in the preamble. The method ends with the identification of the mutant cell, not the obtaining or isolation of said cell. Correction is required.

Claim Rejections - 35 USC § 112-Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "A method of producing a heterologous protein, comprising: transforming a mutant *B.subtilis* cell, wherein said mutant cell comprises a mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, with a recombinant vector comprising a nucleic acid directing synthesis of the heterologous protein and recovering the heterologous protein from the cell"; "a mutant *B.subtilis* cell, wherein said mutant cell comprises a mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, and a recombinant vector comprising a nucleic acid directing synthesis of a heterologous protein"; and "A method of obtaining a mutant *B.subtilis* cell, comprising: making a mutation to the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7", does not reasonably provide enablement for the scope of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification is only enabled for methods which use *B.subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims. It would take one of skill in the art undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus.* Bacterial species often times do not produce the same proteins. The prior art is silent as to whether any other species of Bacillus possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B.subtilis*. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson,

383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Response to Applicants' arguments:

Applicants argue that it would not take undue experimentation to practice the claimed invention. They state that a certain amount of routine experimentation is permissible. They argue that they are enabled for the broad scope of the invention because they have shown in Example 6 that primers based on the *cypx* gene from *B.subtilis* were used to clone by PCR the *cypx* gene from *B.licheniformis* and delete a portion to prevent formation of the red pigment. They further argue that they describe methods for isolating *cypX-yvmC* operons from *B.subtilis* and *B.licheniformis*. They argue that it is within the skill of the art to "discover new red pigment genes in other species of *Bacillus* using Applicants' disclosure. These arguments have been fully and carefully considered but are not deemed persuasive in overcoming the rejection.

The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a

recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in the instant claims possess *yvmC* and/or *cypX* genes. At the very least, the specification has only shown that *B.licheniformis* possesses a the *cypx* gene which can produce red pigment. The prior art is silent as to whether any other species of Bacillus possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B.subtilis*. The specification only enables deleting or mutating the *cypX* and *yvmC* from B.subtilis and the *cypX* gene from *B.licheniformis* in order to get better expression of a heterologous protein. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be

provided in order to enable members of the public to understand and carry out the invention."

Claim Rejections - 35 USC § 112-Written Description

6. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification has only taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification only provides adequate written description for methods which use *B.subtilis* genes and

mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:1 and 7, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and mutant cells. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The product itself is required.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of other species of bacteria and potential genes encoding red pigment proteins is made. This is insufficient to provide Written Description to support the generic claims.

Response to Applicants' arguments:

Applicants state that the arguments to the Written Description were addressed in the arguments to the Enablement rejection. These arguments were addressed above.

Status of Claims:

7. The prior art has taught the complete genome sequence of *Bacillus subtilis.* Further, the prior art teaches hypothetical proteins which are cytochromes and match the protein sequence encoded by SEQ ID NO:1. A hypothetical conserved protein designated yvmC is also deduced from the complete genome sequence and matches SEQ ID NO:8 by 98.8% identity. However, it is not taught that this protein is a red pigment protein.

The prior art does not teach or suggest mutating the cypX gene comprising the nucleotide sequence set forth in SEQ ID NO:1 and/or the yvmC gene comprising the nucleotide sequence of SEQ ID NO:8, much less mutating them in order to stop red pigment production. Mutant bacterial cells comprising these mutated genes are not

taught or suggested by the prior art. The instant claims are free of the prior art, but must overcome the 112, 2nd and 1st rejections before they are deemed allowable.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser 4/5/06
Primary Examiner
Art Unit 1645